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10/613,077	07/01/2003	Devin Leake	13510CIP	6961

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EXAMINER

BOWMAN, AMY HUDSON

ART UNIT

PAPER NUMBER

1635

DATE MAILED: 04/12/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

# Office Action Summary

Application No.

10/613,077

Applicant(s)

LEAKE ET AL.

Examiner

Amy H. Bowman

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

## Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

## Status

- 1) ☒ Responsive to communication(s) filed on 22 February 2005.
- 2a) ☐ This action is FINAL. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

## Disposition of Claims

- 4) ☒ Claim(s) 1-88 is/are pending in the application.
- 4a) Of the above claim(s) 1-34, 41, 55, 69, 80 and 88 is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 35-40, 42-54, 56-68, 70-79 and 81-87 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

## Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 01 July 2003 is/are: a) ☒ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

## Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some \* c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
  - ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  - ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

## Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)  
Paper No(s)/Mail Date 7/6/04, 7/12/04, 12/13/04, 1/10/05
- 4) ☐ Interview Summary (PTO-413)  
Paper No(s)/Mail Date. \_\_\_\_\_
- 5) ☐ Notice of Informal Patent Application (PTO-152)
- 6) ☐ Other: \_\_\_\_\_

### DETAILED ACTION

Applicant's election with traverse of group II, directed to claims 35-87, and cholesterol as the conjugate species, in the reply filed on 2/22/2005 is acknowledged.

Applicant argues that it would not pose an undue burden to examine the asserted claim groups together because each group recites at least one 2' modification. On the contrary, the common structural element of a 2' modification is not sufficient for a search of one of the double stranded polynucleotide inventions to necessarily return art against another. As explained in the official office action mailed 1/27/2005, the inventions of groups II and III are related to the invention of group I as product and process of use. In the instant case, the double stranded polynucleotides of groups II and III, respectively, can be used as probes for identifying the presence of specific mRNA transcripts in *in situ* hybridization assays, which does not involve methods of performing RNA interference, as present in group I. Although each of the inventions comprise a 2' modification, the mere presence of a 2' modification does not render the groups to be one single invention.

The inventions of groups II and III are unrelated, as explained in the official office action mailed 1/27/2005. Although the inventions may each be used for the same purpose, the inventions involve different structural considerations, resulting in the need for a separate search for each invention. For example, the double stranded polynucleotides of group II would not involve a search of the composition of group III, as the composition of group III would not involve a search for the polynucleotides of group

II. Each of these inventions involve separate considerations and would require a separate search.

Applicant traverses the species election requirement on the basis that the specification discloses that each member of the genus increase stability and/or facilitate uptake of RNA. On the contrary, the members of the claimed genus do not contain a common structural core, thereby requiring a separate search for each.

The requirement for restriction is still deemed proper and is therefore made FINAL.

Claims 1-34, 41, 55, 69, 80 and 88 are withdrawn as being drawn to non-elected inventions. Although claims 41, 55, 69 and 80 were elected with group II, they are drawn to a non-elected conjugate. The conjugate group of "lipids" will be examined, which includes cholesterol.

### ***Claim Objections***

Claims 39, 53, 67, 78 and 87 are objected to because of the following informalities: Claims 39, 53, 67, 78 and 87 are not only drawn to the elected conjugate group, lipids, but are also drawn to various other non-elected conjugate groups. Appropriate correction is required.

### ***Claim Rejections - 35 USC § 102***

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 75-77, 81 and 83-86 are rejected under 35 U.S.C. 102(b) as being anticipated by Matulic-Adamic et al. (U.S. 5,998,203).

The instant invention is drawn to an 18-30 nucleotide double-stranded polynucleotide comprising a sense strand and an antisense strand, wherein the strands comprise a conjugate and a 2' modified nucleotide, such as a 2' fluorine modification, and further comprising an overhang and a phosphorothioate linkage.

Matulic-Adamic et al. teach a synthetic ribozyme that meets the structural limitations of a dsRNA. See for example, figure 3, wherein helix 4 can be formed from two separate strands, i.e. without a connecting loop, leaving a dsRNA molecule. Matulic-Adamic et al. teach incorporation of chemical modifications at the 5' and/or 3' ends of one or both strands, as well as various conjugates. The 3'-cap taught by Matulic-Adamic et al. is taught to protect the nucleic acids from exonuclease degradation, resulting in increased half-life of the nucleic acid inside of a cell and improved overall effectiveness of the nucleic acid. A structure is given in column 3 of the specification to depict a 3'-cap wherein X can be a modified base nucleotide, which would result in an overhang on the 3' end. The structure in column 3 is interpreted as having a one-nucleotide overhang. Additionally, Matulic-Adamic et al. teach various modifications to the base, sugar and/or phosphate to promote stability. Specifically, phosphorothioates and 2' modifications such as H, O-alkyl, C-alkyl, halo and NHR are taught. Matulic-Adamic et al. teach 2' halogen modifications wherein the halogen is

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fluorine. The ribozymes taught by Matulic-Adamic et al. are designed to have complementarity to a selected target sequence.

Therefore, the invention of claims 75-77, 81 and 83-86 are anticipated by Matulic-Adamic et al.

Claims 75, 76, 78, 79, 81 and 83-86 are rejected under 35 U.S.C. 102(b) as being anticipated by Agrawal et al. (WO 94/01550).

Agrawal teaches double-stranded RNA structures wherein the molecules can have modified nucleic acid bases and/or sugars, as well as such molecules having added substituents such as cholesteryl or other lipophilic groups (see page 8). Additionally, Agrawal et al. teaches phosphorothioates, ribonucleotides and 2'-O-methyl modifications (see page 16). Agrawal teaches a double stranded RNA structure with overhangs (see figures 1 and 6). Therefore, the invention of claims 75, 76, 78, 79, 81 and 83-86 are anticipated by Agrawal et al.

### ***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Claims 35-40, 42-54, 56-68, 70-79 and 81-87 are rejected under 35

U.S.C. 103(a) as being unpatentable over Amarzguioui et al., in view of Parrish et al., Scaringe et al., and Biegelman et al.

The instant invention is drawn to a double stranded polynucleotide comprising a 18-30 nucleotide, more specifically 19 nucleotide sense and antisense strand, wherein the strands comprise various 2' modifications, lipid conjugates and overhangs, and wherein at least one of said sense strand and antisense strand comprises at least one orthoester modified nucleotides.

Amarzguioui et al. teach 19 (see figure 1) and 21 nucleotide (see abstract) siRNA duplexes, wherein the siRNA strands comprise 2'-O-methylation, 2'-O-allylation or phosphorothioates (see abstract) for increased persistence of silencing. The modifications were tested at the 3' and 5' ends, as well as the non-basepairing 3' overhangs (see page 591). As evidenced by Elbashir et al., such overhangs increase efficiency of target RNA cleavage.

Amarzguioui et al. do not teach orthoester modifications, cholesterol conjugates, or fluorine modified nucleotides.

Parrish et al. teach modified siRNA duplexes. Parrish et al. teach 2'-O-alkyl (i.e. 2'-O-methyl) modifications at various nucleotide positions of the siRNA duplex, as well as 2'-fluorouracil modifications (see figure 5).

Scaringe teaches orthoester protecting groups and their uses with antisense oligonucleotides and ribozymes. Scaringe teaches that orthoester groups alone, as well as in combination with 2'-modifications, help minimize degradation.

Beigelman et al. teach lipid conjugates of biologically active compounds including siRNAs. Cholesterol is an ideal selection for a lipid conjugate, as evidenced by supporting references, Manoharan et al. (see page 9) and Letsinger et al. (see abstract). Beigelman et al. teach that such conjugates improve the bioavailability and pharmacodynamics of a molecule compared to unconjugated molecules. Beigelman et al. teach a wide array of conjugates including lipids, small molecules, polyethylene glycol and protector groups. Additionally, Beigelman et al. teach modification of nucleic acid molecules to enhance stability by modification with nuclease resistant groups, for example, 2'-allyl, 2'-fluoro, 2'-O-methyl as well as phosphorothioates. The modifications and conjugates taught by Beigelman et al. are applicable at various locations of the nucleotide.

It would have been obvious to incorporate a fluorine modification as taught by Parrish et al. and Beigelman et al., to incorporate an orthoester group as taught by Scaringe, and to incorporate a lipid conjugate as taught by Beigelman et al. with the motivation of improving the pharmacodynamics of the molecule, enhancing stability and minimizing degradation, as taught by the references above.

There would have been a reasonable expectation of success to incorporate an orthoester group, cholesterol conjugate or fluorine modified nucleotide into the siRNA duplexes taught by Amarzguioui et al., as taught by Scaringe, Beigelman et al. and Parrish et al. and for the benefits cited therein since these features are minor modifications to the dsRNA duplex and each were known in the art at the time the

invention was made. Based on the prior art, there is no evidence that these modifications would not work in combination to provide the benefits cited of the prior art.

Thus in the absence of evidence to the contrary, the invention as a whole would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Amy H. Bowman whose telephone number is 571-272-0755. The examiner can normally be reached on Mon-Fri 7:30 am – 4:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Andrew Wang can be reached on 571-272-0811. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.


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